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Original Article

Adding rosiglitazone to metformin in patients with type 2 diabetes: Effect on diabetes control and metabolic parameters

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ABSTRACT

Aim: To evaluate the efficacy and tolerability, any changes in lipid parameters including free fatty acids and effect on weight and blood pressure, of adding Rosiglitazone to patients with type 2 DM who are not adequately controlled on maintenance dose of Metformin.

Methods: Prospective study of 14 patients with type 2 DM who were maintained on Metformin alone (1.5–2.5 g/day). Twelve patients met the inclusion criteria, and received 4 mg of Rosiglitazone daily in addition to Metformin. Patients were followed for 24 weeks and seen for 6–7 visits. The dose of Rosiglitazone was increased after 8 weeks if FBG was still ⩾160 mg/dl. Full biochemical evaluation was done and safety parameters were observed at base line, at intervals during the study and at the end of the study. All patients completed the study. *T* test was used for comparison.

Results: Eight males and four females were studied. They had the following characteristics: Mean age was (52 ± 6.9) years, weight was (78.2 ± 10.1) kg BMI was (28 ± 4) kg/m^2, waist circumference was (97.5 ± 6.5) cm, and duration of DM was (7.3 ± 6) years. Four patients required an increase of Rosiglitazone dose to 8 mg after 8 weeks.

All patients showed improvement of HbA1c levels by the end of the study. When mean base line parameters were compared to those at the end of study: HbA1c level dropped from (8.9% ± 1.5) to (7.1% ± 1.1) (*P*: 0.00003) and FBG from (205 ± 50.6) to (150 ± 28) mg/dl (*P*: 0.002). Free Fatty Acids (FFA) dropped from (703 ± 213) to (510 ± 303.6) by 8 weeks and to (574 ± 184.6) μeq/L by the end of the study, (*P*: 0.01 and 0.06, respectively). Improvement in HbA1c did not however correlate with the level of FFA drop. There was also significant increase in HDL level (1.15 ± 0.14)–(1.27 ± 0.2) mmol/L, (*P*: 0.02), and weight (78.2 ± 10.1)–(80.1± 10.9) kg (*P*: 0.01). The changes in LDL (3.02 ± 0.57)–(3.23 ± 0.5) mmol/L, TG (2.16 ± 1.1)–(2.2 ± 1.33) mmol/L, waist circumference (97.5 ± 6.5)–(99 ± 8.1) cm, and BP (132.5 ± 17)–(130.2 ± 18.8) mm Hg (systolic), were not significant.

When "Good Responders", (HbA1c drop of >1.5%), (nine subjects) were compared to those with less than 1.5% drop (three subjects), there were no specific characteristics to define responders.

Conclusion: Rosiglitazone, added to Metformin in type 2 DM patients, was effective and well tolerated. There was a significant decrease in FFA levels with treatment. The response to treatment, however could not be predicted from biochemical or clinical parameters. A larger study may be needed to define responder characteristics.

1. Introduction

The use of an insulin sensitizer as a first line oral agent in the treatment of type 2 diabetes mellitus (T2DM) is widely accepted and may have an advantage over the use of an insulin secretagouge.

Metformin has been frequently advocated as a first line agent, especially in obese type 2 DM patients with mild to moderate hyperglycemia. The safety of Metformin has been well established [1].

Most type 2 DM patients however, would require an addition of a second and frequently a third agent with the progression of their DM [2]. Eventually many patients with type 2 DM would require insulin during the course of their disease [3].

Patients who present with moderate to severe hyperglycemia may require two oral agents or insulin at the onset. Using two oral hypoglycemic agents of different classes of actions simultaneously as a first line treatment of type 2 DM has also been considered recently for better and more efficient control with fewer side effects [4].

Thiozolidinediones is a group of relatively recent oral hypoglycemic drugs with novel mechanism of action. Although the exact mechanisms of action for those drugs are still being investigated,

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they seem to work primarily by stimulating the nuclear receptor PPAR gamma which mediates or affects carbohydrate metabolism. The effect on the PPAR alpha that alters lipid metabolism is less pronounced. They can also decrease peripheral resistance and improve glucose uptake especially in muscle and adipose tissue [5]. These agents can also decrease gluconeogenesis by improving liver insulin sensitivity [6]. Some of the Thiozolidinediones actions may be mediated by a decrease in free fatty acid level [7].

The efficacy of Thiozolidinediones was shown in number of studies as single agents [8], or in combination with Metformin or Sulfonyureas [9–11]. Regional, smaller size studies were also conducted in some countries and found Rosiglitazone to be beneficial in patients with type 2 diabetes who were not controlled on a combination of Sulfonylurea and Metformin [26], or when added with sulfonylurea and Metformin to type 2 patients who were not well controlled on insulin [27].

The specific advantage of these drugs over others are emerging with the ability to preserve and improve β cell function. Although the long term clinical effects of Glitazones on cardiovascular risk in patients with diabetes have not yet been proved, studies did show significant improvement in markers such as Adiponectin and a decrease in inflammatory markers like C Reactive Protein (CRP), Tumor Necrosis Factor (TNF) and Resistin [12]. In the PRO active study, pioglitazone was shown to significantly reduce the composite of all causes of mortality, non-fatal myocardial infarction, and stroke (secondary end point) in high risk type 2 DM patients [13].

MORE ABOUT THIS STUDY

Free fatty acids and other metabolic parameters were monitored throughout the study.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

Rosiglitazone was shown to be effective and relatively safe when added to other oral agents like Metformin in type 2 DM patients. Recent but still controversial data, however, cautions a possible increase in cardiovascular events in patients taking Rosiglitazone.

WHAT THIS STUDY ADDS

The efficacy and relative safety of adding Rosiglitazone to Merfomin in type 2 DM patients were tested in local population.

The study confirms the efficacy & the relative safety of the addition of Rosiglitazone to Metformin in this group of type 2 DM patients. The drop in free fatty acids did not correlate with response, which might argue for additional mechanisms of action.

These agents however are not without side effects, most notably mild to moderate weight gain, due to water retention especially if combined with insulin (Rosiglitazone not indicated for such combination) or due to redistribution of body fat [14]. Decreased bone density [25] and an increased incidence of heart failure were also reported with rosiglitazone [22–24].

In a recent meta-analysis of two large and a few smaller studies using Rosiglitazone, authors found an increase in the risk of myocardial infarction associated with treatment with rosiglitazone [22]. Interim analysis of another trial (RECORD) also found a small, though non-significant increase in the risk of cardiovascular events (composite of hospitalization and death from cardiovascular causes) [23,24]. More careful post marketing studies are therefore needed to address this new issue.

A study on the use of Rosiglitazone in patients with type 2 DM taking Metformin was performed previously [10,11], and indicated that the combination of Rosiglitazone and Metformin is safe and effective.

This study was thus conducted to examine the effect and safety of this combination in a local population (part of multicenter international protocol in Middle Eastern and North African countries). We have analyzed the data on patients studied at our center.

2. Patients and methods

Patients aged between 40 and 80 years with type 2 DM (according to American Diabetes Association (ADA) criteria), for at least 3 month, who had been on Metformin (1.5–2.5 g/D) for at least 3 month before enrollment in the study, but not adequately controlled, were recruited from the family clinics of the King Faisal Specialist Hospital & Research Center. Patients with pregnancy, major medical problems, heart failure, liver or renal dysfunction, elevated creatinine, more than 133 μmol/L for male or 124 μmol/L for female or ALT, AST, or Alk Phosphatase higher than 2.5 times the upper normal limit, were excluded. Women at reproductive age had to be on contraceptives. Fourteen patients who were on Metformin alone were identified and screened for the study after taking their consent. All patients had screening visit with full clinical evaluation, medication history, physical examination, and chemistry labs with urine HCG if indicated and base line ECG.

Patients dietary habits were evaluated and basic dietary instructions were provided by a dietician, only if needed. Most of the patients were fairly active though they did not take exercise regularly. No recommendations were made for any change in the level of activity during the study period. Laboratory tests included full chemistry profile (including CBC, electrolytes, renal, and hepatic function tests), Fasting Blood Glucose (FBG), lipid profile, urine analysis and free fatty acid levels. All biochemical studies were done at our laboratory using automated Roche Modular P 800. The free fatty acid levels were determined at the Mayo clinic laboratory (Rochester, Minnesota) using enzymatic colorimetric assay. At the base line visit, which was 2 weeks after the screening visit, Laboratory tests were repeated and patients received 4 mg of Rosiglitazone daily in addition to their usual dose of Metformin, if FBG was equal or more than 140 mg/dl but less than 300 mg/dl and others were excluded. Twelve patients met the inclusion criteria. Patients were followed for 24 weeks and seen for 6–7 visits. The dose of Rosiglitazone was increased after 8 weeks (visit 4) if FBG was still $\geqslant$160 mg/dl. Full biochemical evaluation and safety parameters were done at screening visit, base line visit, visit 4, and at the end of the study. Clinical evaluation, evaluation of side effects, vital signs, waist measurements and fasting glucose were done in all visits. All patients remained on their usual medications during the study. All patients completed the study. Good responders were defined as those with Glycosylated (HbA1c) drop of $\geqslant$1.5%. T test was used for comparison. The study was approved by the medical research council and the ethics committee of our center.

3. Results

All patients (eight male and four female) completed the study. The patient characteristics at base line are summarized in Table 1.

When mean base line parameters of patients were compared to those at the end of study; HbA1c level dropped from 8.9% ± 1.5 to 7.1% ± 1.1 (P: 0.00003), and FBG from 205 ± 51.6 to 150 ± 28 mg/dl (P: 0.002). FFA dropped from 703 ± 213 to 510 ± 303.6 μeq/L by 8 weeks and to 574 ± 184.6 μeq/L by the end of the study, (P: 0.01 and 0.06, respectively) (Figs. 1–3).

There was no correlation, however, between the improvement in HbA1c and the level of FFA drop. Four patients required an increase of Rosiglitazone dose to 8 mg at week 8 of the study, because FBG was higher than 160 mg/dl.

Table 1
Characteristics of the 12 patients in the study at base line, mean with standard deviation and (range).

Age (years)	52 ± 6.9 (44–67)
Weight (kg)	78.2 ± 10.1 (64–95)
BMI (kg/m^2)	28 ± 4 (22.7–35.5)
Waist diameter (cm)	97.5 ± 6.5 (87–109)
Duration of DM (years)	7.3 ± 6 (1–20)

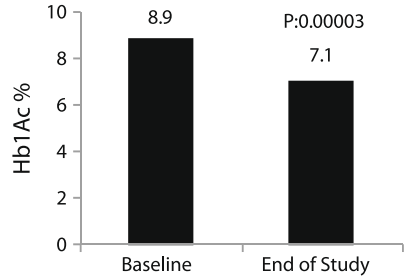

Fig. 1. Mean HbA1C level of patients at base line and at the end of the study.

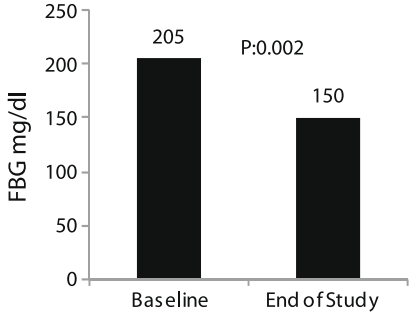

Fig. 2. Mean FBG level for all patients at base line and at the end of the study.

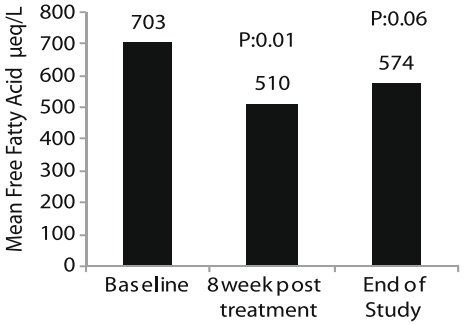

Fig. 3. Mean free fatty acid levels (µeq/L) for all patients at base line, 8 weeks and at the end of the study.

All patients showed improvement of HbA1c levels by the end of the study (range 0.2–3%). Two patients had a drop of HbA1c levels of less than 1 (0.2% and 0.4%) and one patient had a drop of 1.3%, while nine patients had a drop of more than 1.5%.

There was also a significant increase in High Density Lipoprotein (HDL) levels, and a mild but significant increase in weight after treatment. Low Density Lipoprotein (LDL), Triglyceride (TG), waist circumference, and Blood Pressure (BP) did not show significant changes (Figs. 4–6).

When "Good Responders" (nine subjects) were compared to those with less than a 1.5% drop in HbA1c (three subjects), there were no specific characteristics to define responders, although

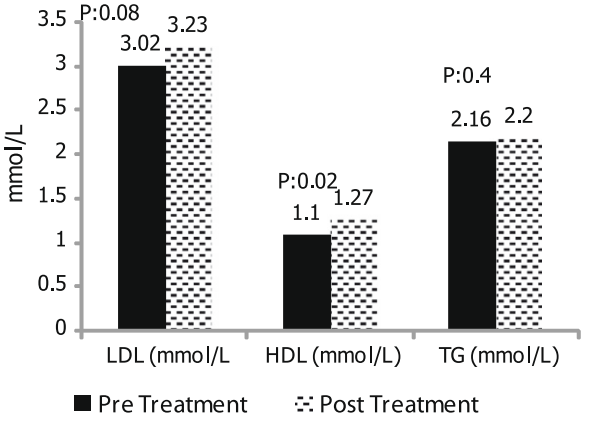

Fig. 4. Mean LDL, HDL, and TG levels for all patients at base line and at the end of the study, there were no significant changes in LDL and TG levels, but a significant increase in HDL.

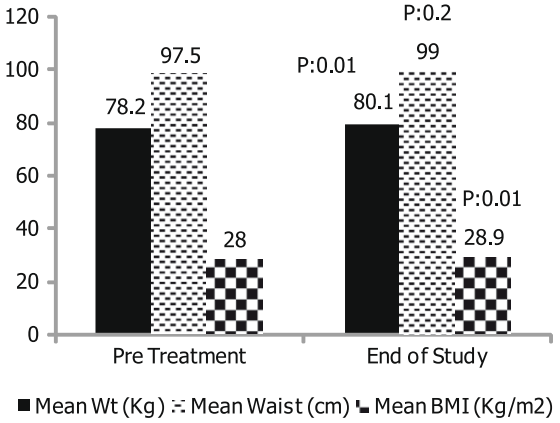

Fig. 5. Mean weight, BMI and waist diameter for all patients at base line and at the end of the study, there was mild but significant gain of weight and increase in BMI at the end of the study, but no significant change in waist diameter.

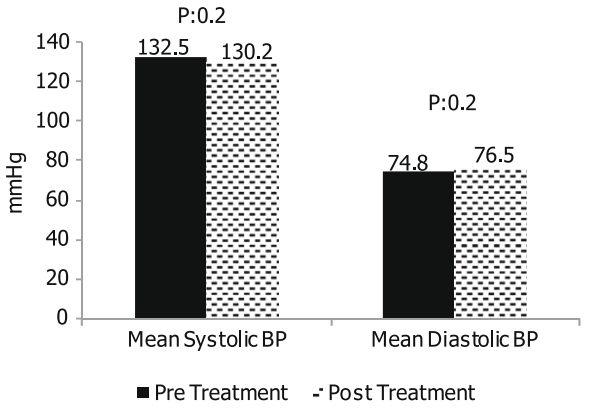

Fig. 6. Mean systolic and diastolic BPs at base line and at the end of the study. There was no significant change in BPs.

"Good responders" tended to have lower FFA levels at base line (*P*: 0.06), and to have higher Body Mass Index (BMI) and HbA1c at base line (Table 2).

4. Discussion

Insulin resistance and impairment in insulin secretion are important factors in the pathophysiology of type 2 DM. The

Table 2
Comparison of the characteristics of better responders (HbA1c drop of ⩾1.5%) and those with less response.

	Good responders	Others	*P* value
Base line (weight)	79.1	75.3	0.2
Base line BMI (kg/m^2)	28.6	26.3	0.1
Age (years)	52.4	50.6	0.3
DM duration (years)	8	5.3	0.2
Base line FBG (mg/dl)	196	231	0.2
Base line HbA1c (%)	9.1	8.4	0.2
Base line FFA (μeq/L)	628	926	0.06
End of study FFA (μeq/L)	589	529	0.2

contribution of each factor may vary from one patient to another or even during the natural progression of the disease in the same patient [28,29].

The advantages of using oral agents that are primarily insulin sensitizers over those that are insulin secretagouges are lower blood insulin levels and less or no hypoglycemia [30]. The effects of insulin secretagouges also wane with time due to decreasing ability of these agents to stimulate insulin secretions from β cell. The use of Rosiglitazone was associated with less failure as mono-therapy than Metformin and Glyburide in a recent large trial (ADOPT) [19]. Another trial (DREAM) found Rosiglitazone to be effective in reversing those with mild early diabetes to a pre-diabetic stage [20,21].

The combination of Thiozolidendione and Metformin as an initial or sequential treatment of type 2 DM may have significant clinical advantages. The two agents work in two different mechanisms of decreasing peripheral resistance at the muscle level and in decreasing hepatic glucose output respectively. Both of them do not induce hypoglycemia or increase insulin secretion. The presence of Glitazone has the advantage of preserving endogenous insulin secretion for a longer period as compared to those on secretagogues [8]. Side effects may be less with smaller doses of Glitazones in combinations with Metformin, especially in terms of weight gain. In one study, the addition of Rosiglitazone was found to result in better control than an escalating Metformin dose in type 2 DM patients with suboptimal control on Metformin alone [15]. Our results indicated a good efficacy for the drug in our patients, with 10 patients out of 12 having more than a 1% drop in their HbA1c levels, and 9 with 1.5 points or more drop. These results are comparable or better than generally published international data [9–11]. There are number of possibilities to account for this success in our patients: *First*; the average HbA1c level at base line is rather high which indicates a worse control at base line than generally reported in similar studies, which can result in a sharper drop of HbA1c levels to the additional treatment. *Second*, the patients were followed closely, and might have become more motivated to achieve better control. However, it is equally feasible that Glitazones exert better effect on certain patients than others, and that we had a larger proportion of good responders in the group studied. We attempted to identify the characteristics of good responders by comparing those with an improved HbA1c of 1.5% or more, to others with less than 1.5% drop. There were no significant differences between the two groups. The number of patients, especially those with less response, was however too small for meaningful comparison. Nevertheless, it was noted that the base line FFA was lower in the better responders ($p = 0.06$). This may indicate less insulin resistance in this group.

It is interesting to note that the level of response did not correlate with the drop of free fatty acid levels, in spite of a significant decrease in its level, especially after 8 weeks of treatment.

The small number of patients in this study, and the heterogeneity of patient responses, might account for this lack of correlation. Other mechanisms of action may also be responsible for the Rosiglitazone effect, such as the effects on beta-cell function and insulin sensitivity [5–7].

In the "A Diabetes Outcome Progression Trial" (ADOPT) study, Rosiglitazone was found to be more effective than both Glibenclamide and Metformin in sustaining glycaemic control in the long-term with the greatest response observed in older patients (>50 years) and those with a higher base line BMI (>30) and larger waist circumference (>110 cm) [19], a trend that we saw in our studied patients.

Our patients also tolerated the treatment well. There were no major side effects attributed to the addition of Rosiglitazone in our patients, and the drug was not discontinued in any of our 12 patients. In one of the patients with underlying mild valvular heart disease and history of bronchial asthma, an increase in shortness of breath occurred for a period after increasing the dose of Rosiglitazone to 8 mg. In this patient, investigations pointed to asthma exacerbation and symptoms resolved after a short period without changing the dose of Rosiglitazone. Nevertheless, there was mild to moderate weight gain in most of the patients, with a mean increase of 1.9 kg (range −1.5 to 5.8 kg). Weight gain is reported to occur with all Thiozolidinedione agents, but seems to be less when these agents are combined with Metformin [10,11]. Weight gain is usually attributed to mild water retention (more when these agents are used with insulin) and to fat tissue redistribution from central to peripheral sites. Improvement of DM control can also be associated with some increase in weight [31]. In our patients, there was no correlation between the degree of weight gain and the response to treatment. The better responders gained 1.7 kg on average, whereas the poor responders gained 2.6 kg on average.

Rosiglitazone can be associated with mild increase in total cholesterol, LDL and TG [11,16]. In this study, however, there were no significant changes in LDL or TG levels. It is of interest that there was a small but significant increase in HDL levels in our patients. Others have also reported favorable effects on lipids and inflammatory markers [16]. We also observed no change in BP in our patients. Other reports also showed little or no change in blood pressure or even a decrease after the use of Glitazones [17,18].

There were no significant changes in liver enzymes in our patients, which is in agreement with other studies on Rosiglitazone and Pioglitazone [10,11].

In summary, we believe that our study, though limited by its small size, supports larger randomized controlled studies in showing the advantage and relative safety of the addition of Rosiglitazone to Metformin in patients with type 2 DM who are not well controlled on Metformin alone. It is reasonable, however, considering the short duration of our study and the recent data on potential cardiovascular risks [23,24], to use judgment and caution when monitoring therapy with Rosiglitazone in a patient with high cardiovascular risk.

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